Management of Richter's transformation

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DISCLOSURES OF COMMERCIAL SUPPORT

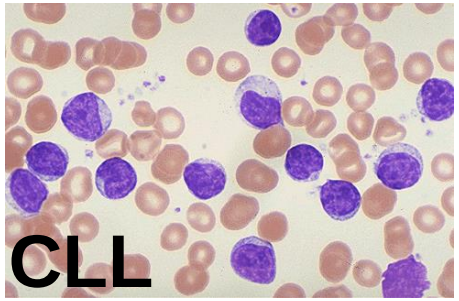
Name of Company	Research support	Employee	Consultant	Stockholder	Speaker's Bureau	Scientific Advisory Board	Other
AbbVie	X					X	
AstraZeneca	X					X	
BeiGene	X		X			X	
BMS						X	
Janssen	X					X	
Lilly			X			X	
MSD						X	

Disease definition

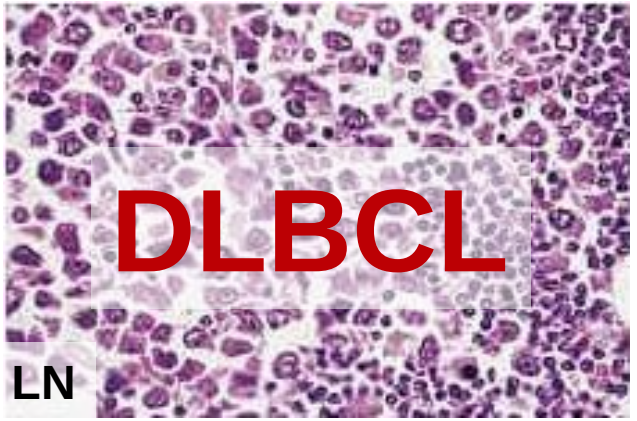
Richter syndrome

Syndromic features

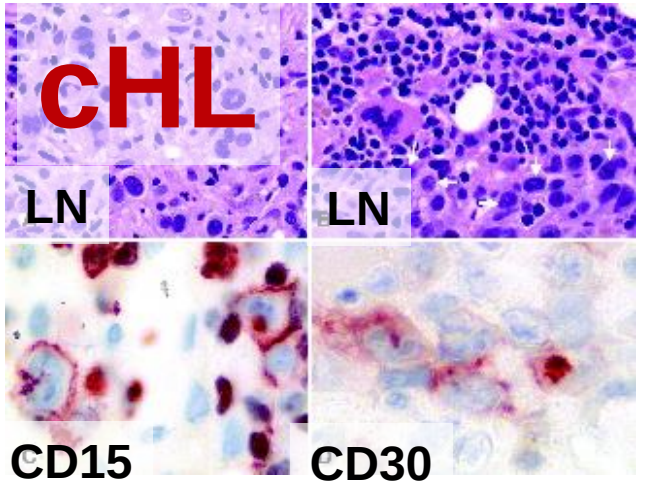
- B symptoms
- Very fast-growing lymph nodes
- Very high LDH
- Hypercalcemia
- High SUV



95-99%



1-5%



After pathology review 30% of cases diagnosed with RT have instead CLL

ICC and WHO-HAEM5

Initial assessment

My practice

Pathology revision to confirm the diagnosis of LBCL-type of RT

- Rare, lack of biomarker, no consensus on criteria (e.g., how many large cells? size of the sheets?)
- Differentiation from mimickers that do not need intensive therapies:
  - Histologically aggressive CLL
  - CLL with HRS-like cells
  - cHL-type RT
  - Pseudo-RT

Clonal relationship between CLL and LBCL

- Clonally unrelated LBCLs do not need intensification if they respond well to R-CHOP
- Comparison of the clonality peaks between CLL and LBCL (blood and/or marrow are source of CLL)

Disease staging is a combination of CLL and LBCL criteria

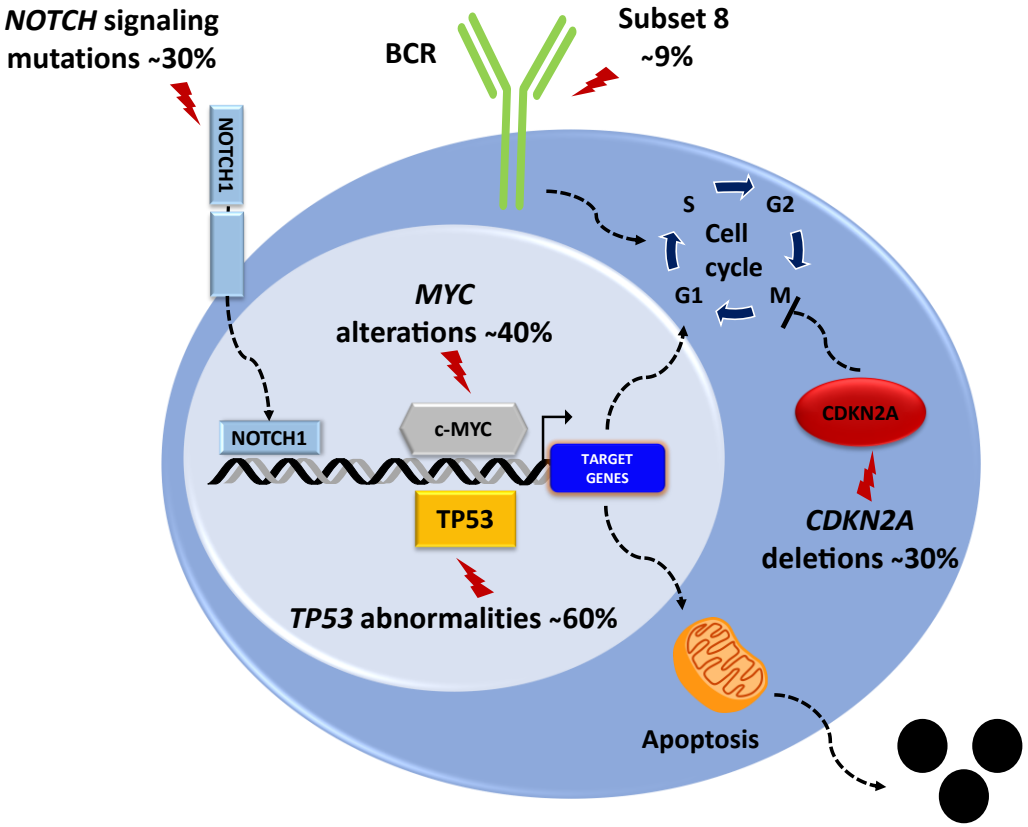
- CE-PET scan
- Bone marrow biopsy

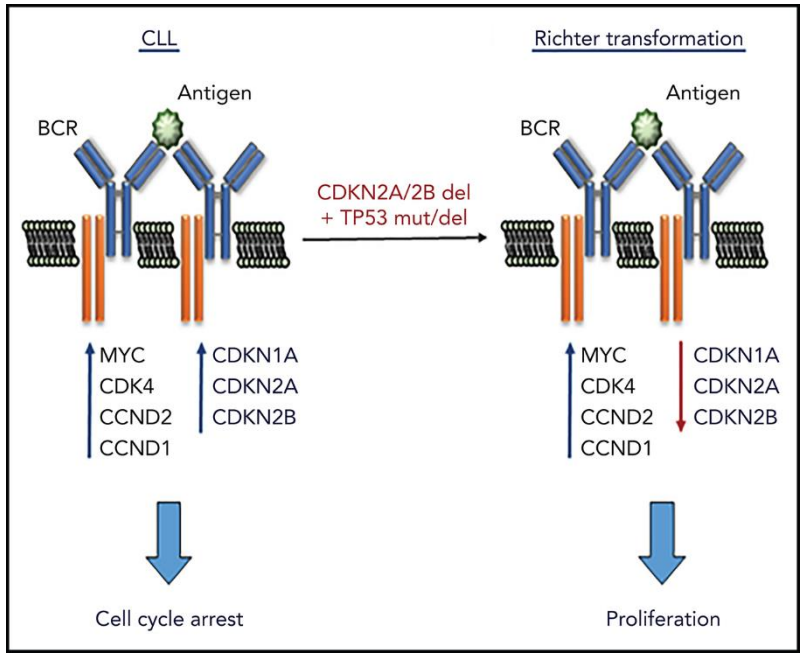
Prognostic biomarkers

- Mutations of *TP53*, *BTK*, *PLCG2*, *BCL2* in both CLL and LBCL samples

Treatment

Proliferation and apoptosis are the master deregulated programs in RT





Chakraborty S, Blood. 2021

Rapidly progressive kinetics
Chemorefractoriness

Adapted from Rossi D, *et al. Semin Oncol* 2016; 43:311–319.

Nadeu F, Nat Med. 2022

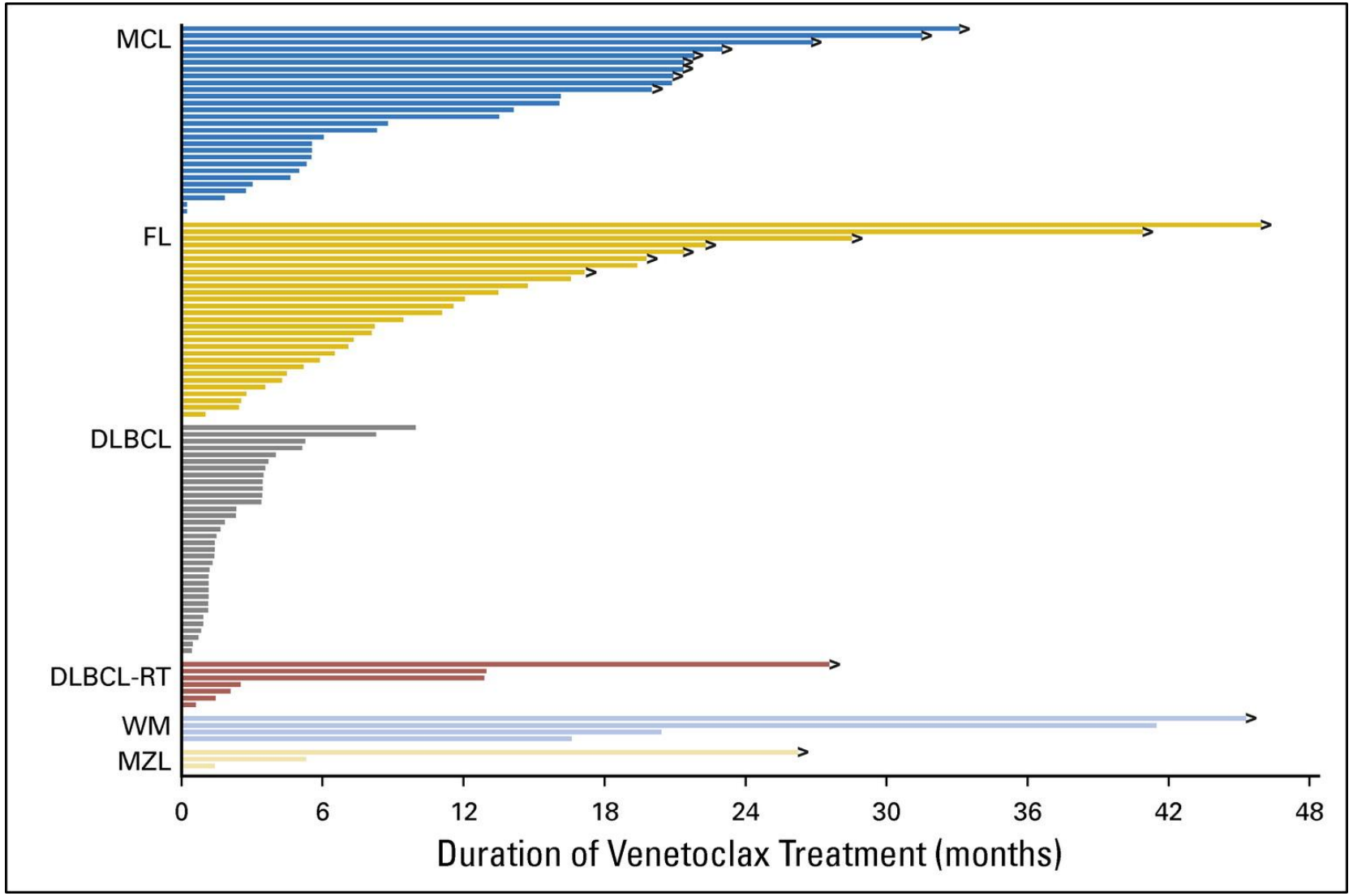
Chemotherapy has limited efficacy in RT

Reference	Patients	Regimen	ORR	CR	PFS (mo)	TRM
Tsimberidou, 2003	30	R+hyper-CVXD	43%	38%	-	18%
Tsimberidou, 2008	35	OFAR1	50%	20%	3	3%
Tsimberidou, 2013	31	OFAR2	38%	6%	3	8%
Durot, 2015	28	DHAP, ESHAP	43%	25%	1	NA
Langerbeins, 2014	15	R-CHOP	67%	7%	10	3%
Eyre, 2016	37	CHOP-O	46%	27%	6	0%
Rogers, 2017	46	R-EPOCH	-	20%	3	NA

RT is sensitive to venetoclax

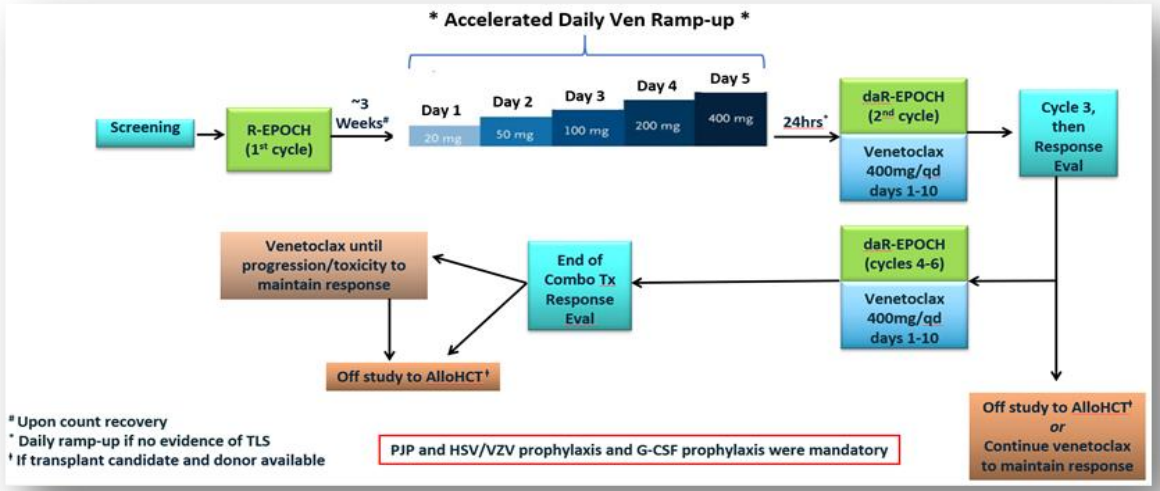
N=7

ORR 43%



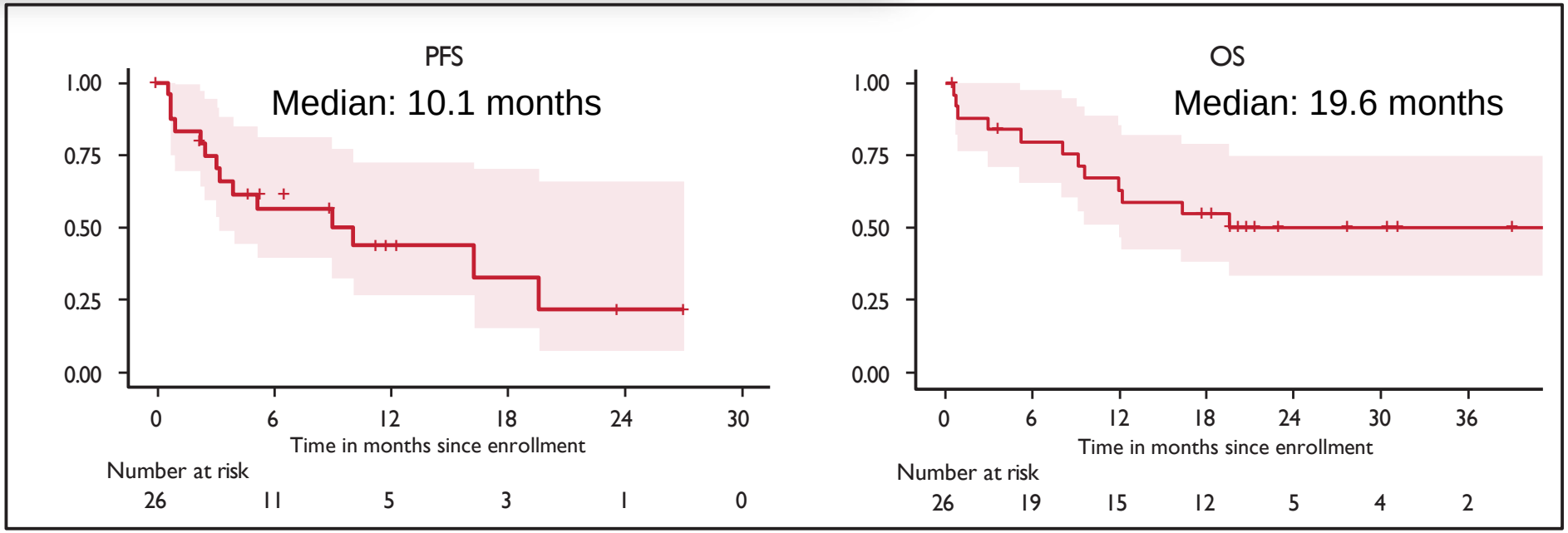
Davids MS, et al. J Clin Oncol. 2017;35:826-833.

Venetoclax DA-EPOCH-R



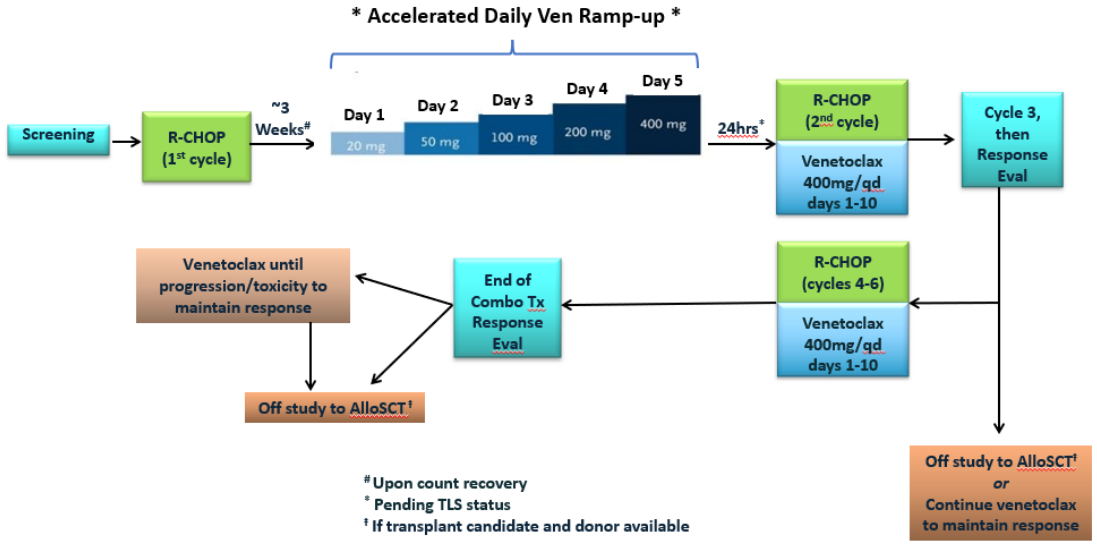
Efficacy summary (n=26)
ORR: 62%
CR: 50%
9 pts in remission electively went to alloHCT

Safety summary
≥Gr 3 heme toxicity: neutropenia (65%), thrombocytopenia (50%)
≥Gr 3 non heme toxicity: febrile neutropenia (26%)
1 pts has died due to infection



Davids et al. Blood, 2022

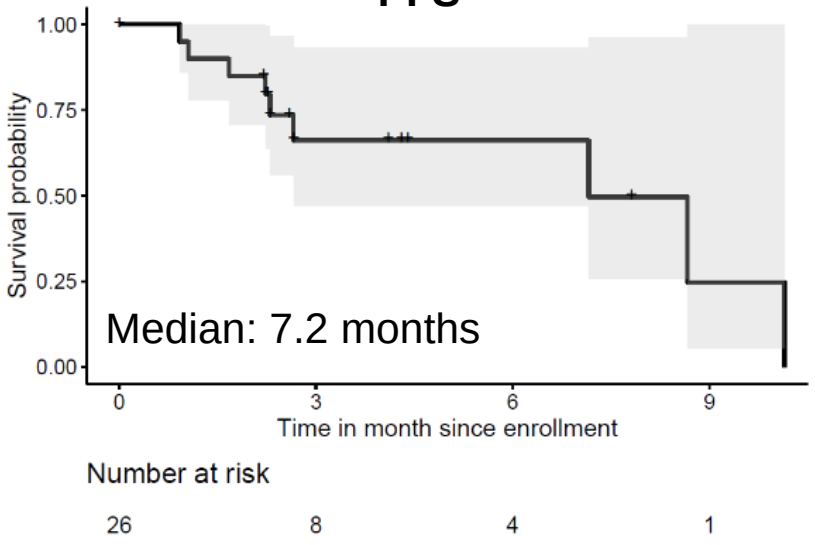
Venetoclax R-CHOP



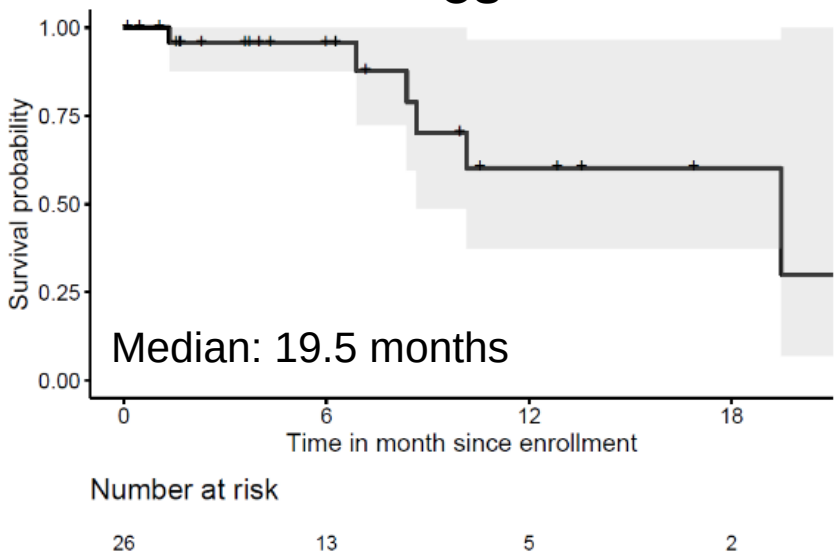
Efficacy summary (n=25)
ORR: 68%
CR: 48%
7 pts in remission electively went to alloHCT

Safety summary
≥Gr 3 heme toxicity: neutropenia (36%), thrombocytopenia (40%)
≥Gr 3 non heme toxicity: febrile neutropenia (32%)
3 pts have died due to infection

PFS



OS

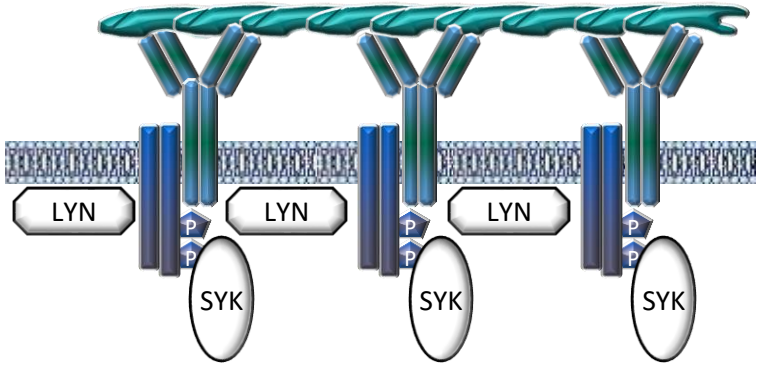


Davids et al. ICML, 2023

Use of subset 8 of the BCR is common in RT

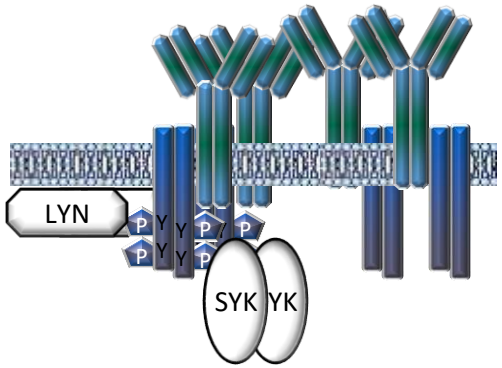
External antigens

Autoantigens exposed on apoptotic cells



Cell autonomous BCR signal

Interaction between of one BCR with another BCR that functions as an autoantigen



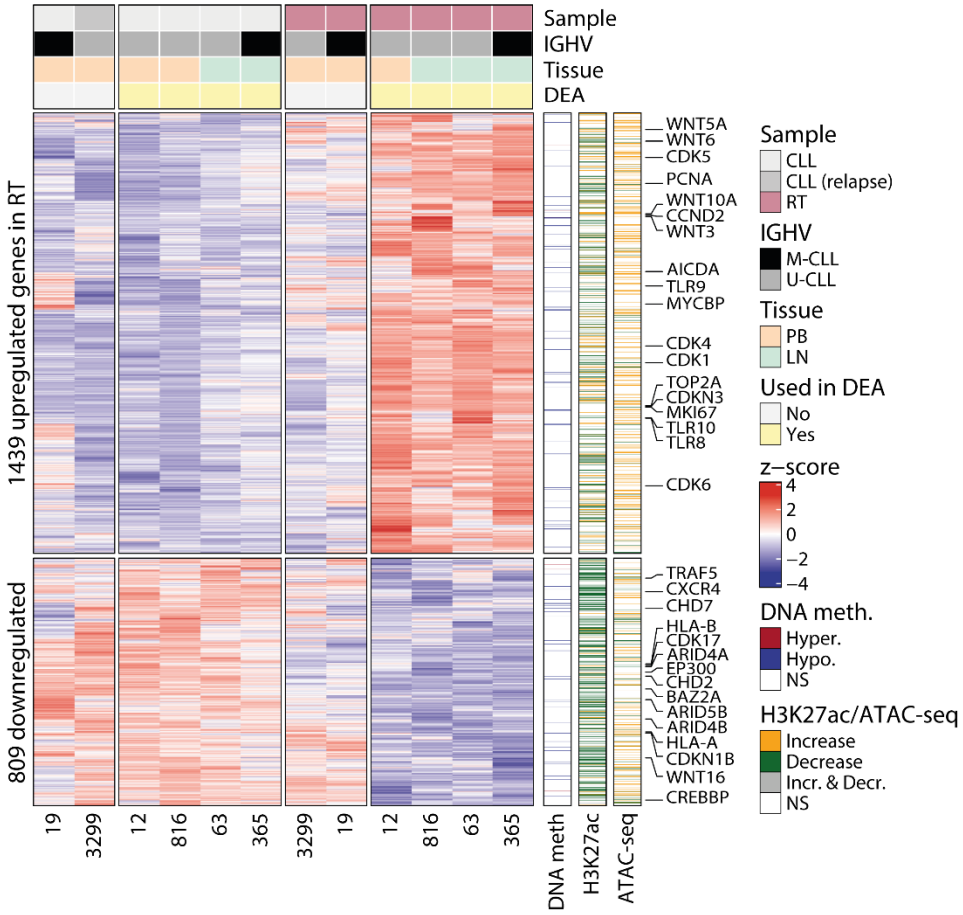
BTK

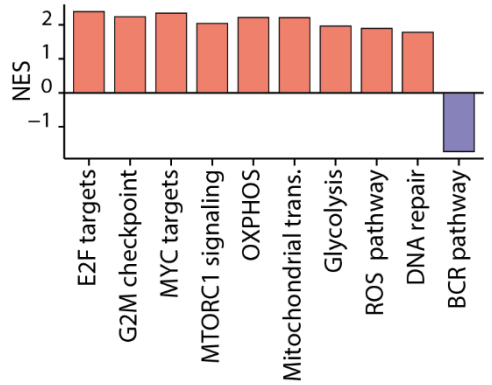
Substet #8

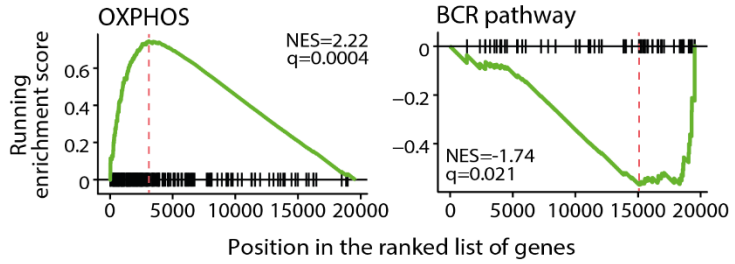
- 0.5% of CLL
- 10% of Richter syndrome
- IGHV unmutated
- Extreme antigen polyreactivity
- Strong phosphorylation of PLCγ2 and ERK1/2

Rossi D, et al, Clin Cancer Res 2009; Chu, et al, Blood 2011; Rossi D, et al, Blood 2013; Gounari M, et al, Blood 2015; Minici C, Nat Commun. 2017; Jaramillo S, Haematologica. 2019

The OXPHOS^{high}-BCR^{low} transcriptional axis of RT



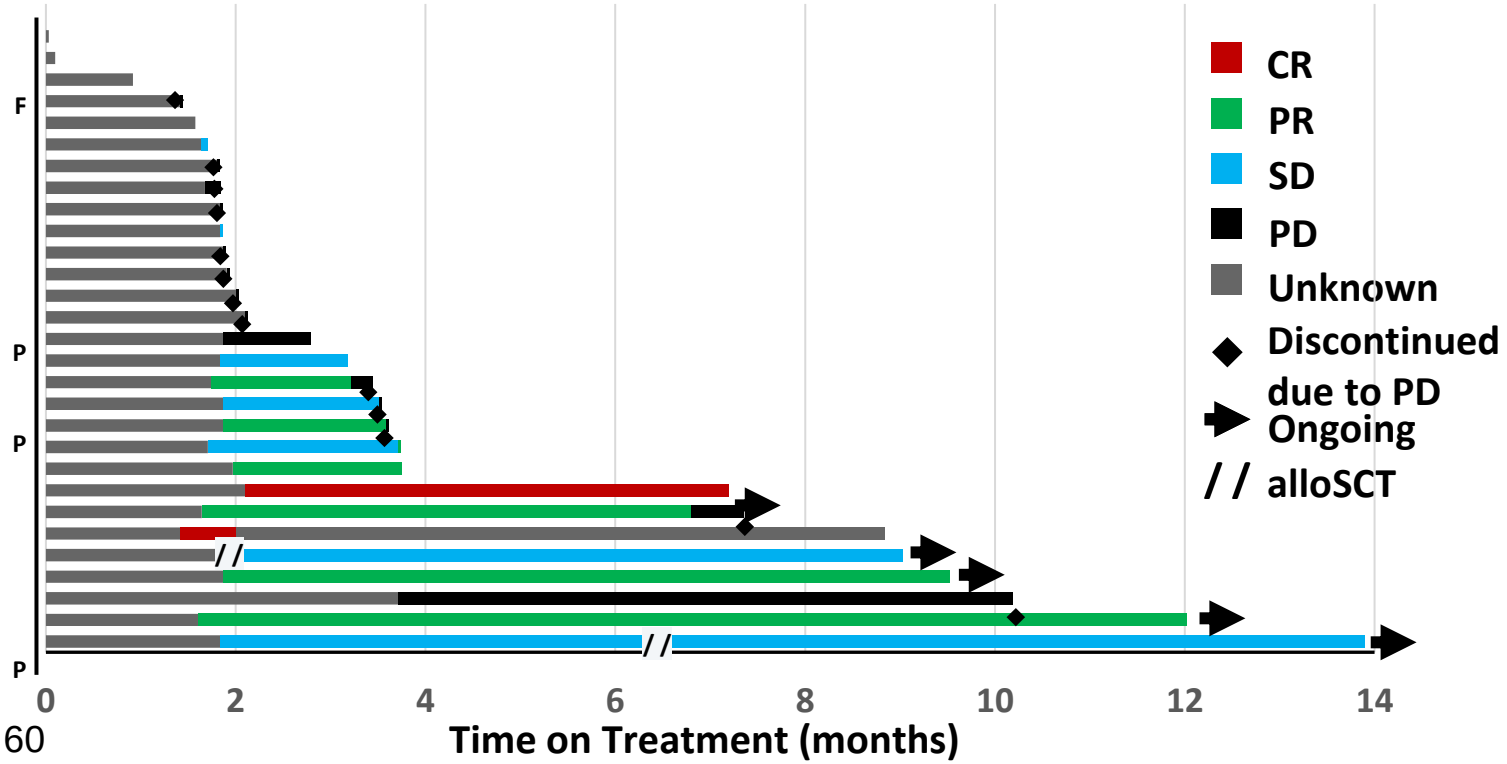




Nadeu F et al Nat Med 2022

Acalabrutinib in RT

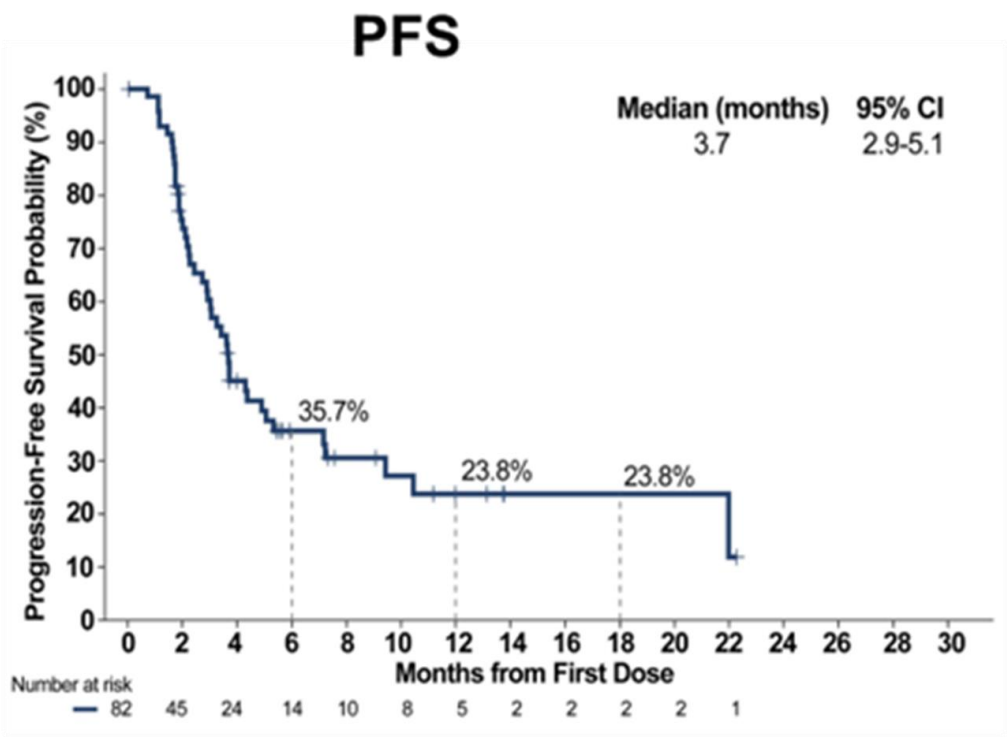
- N=29
- ORR 38.1%
- Median DOR: 5.2 months
- Median PFS: 2.1 months

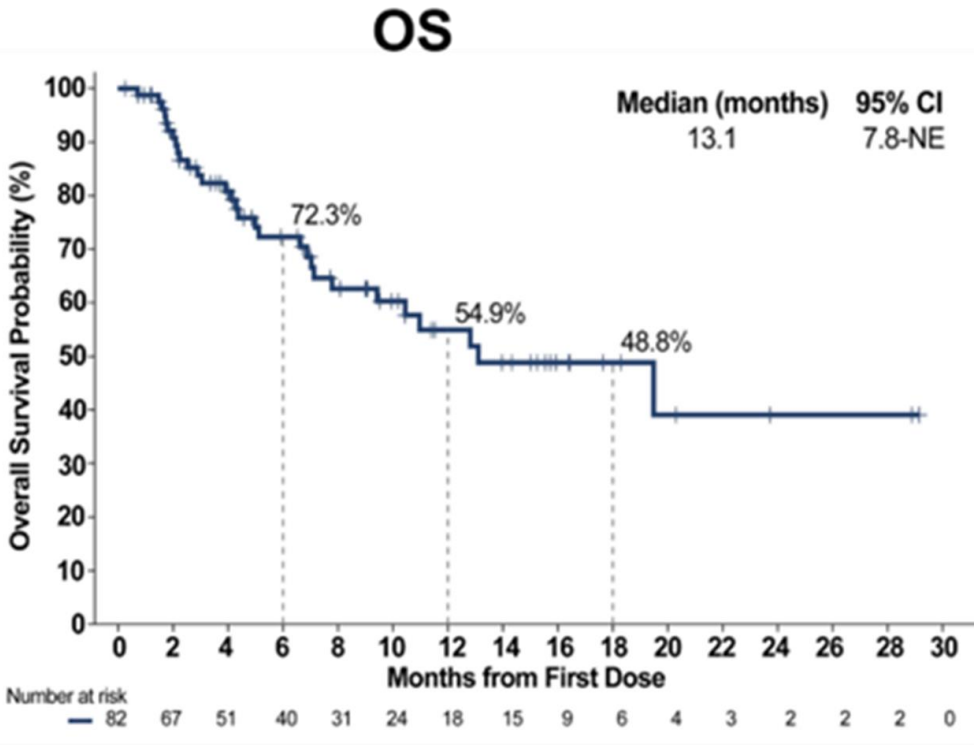


Hillmen P, Blood. 2016:128: 60

Pirtobrutinib in RT

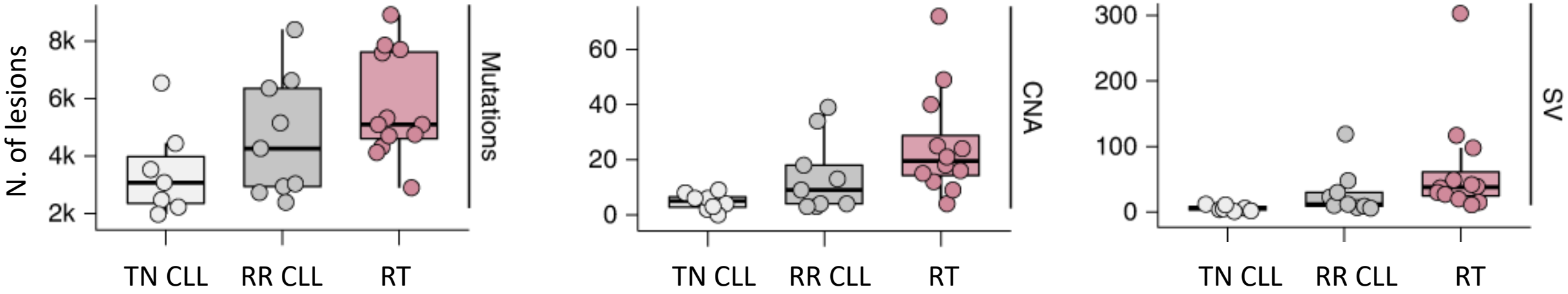
N=82
ORR: 52%
CR: 0%





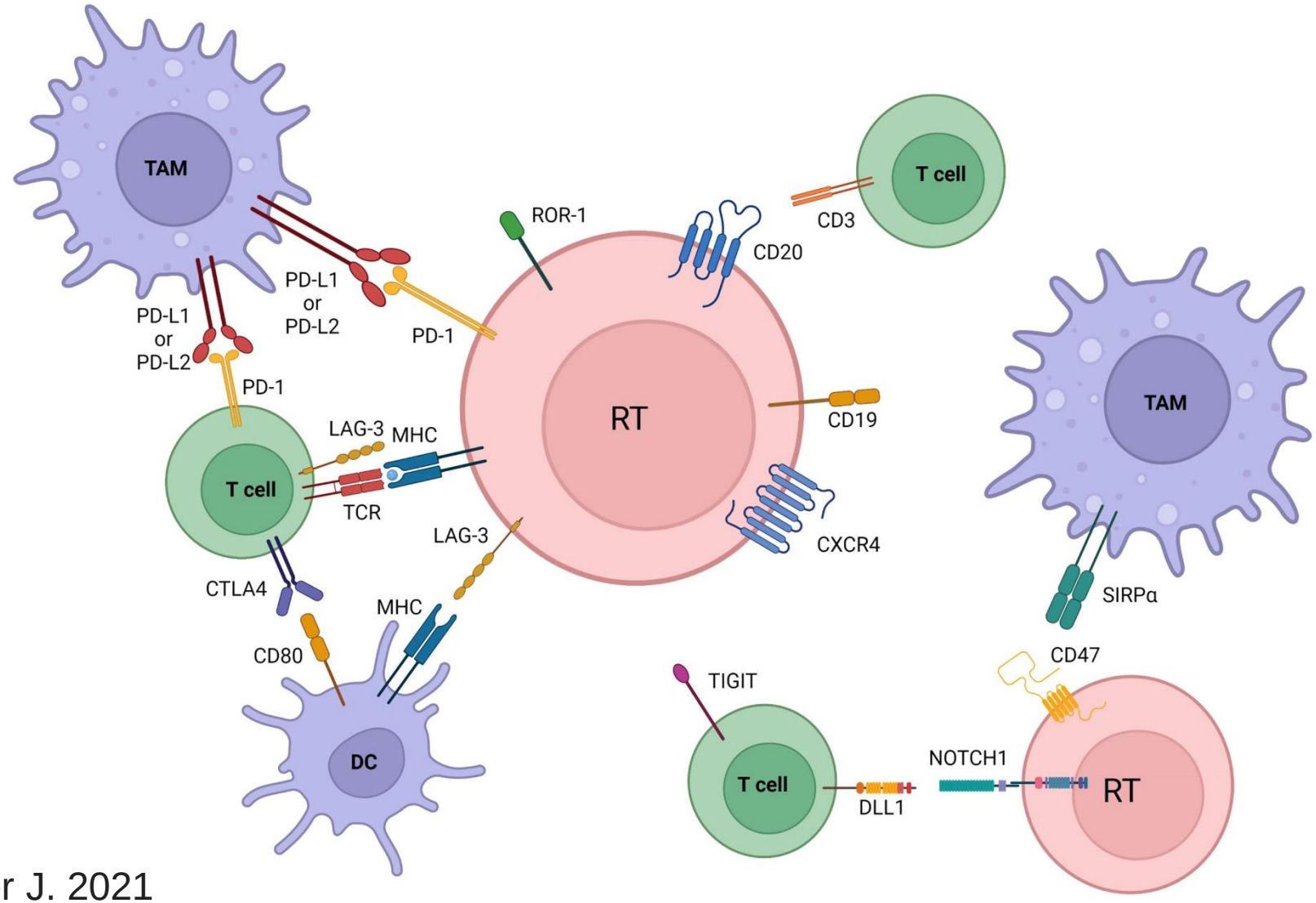
Rhodes JM, AACR 2023

RT is genetically complex (implication for neoantigens?)



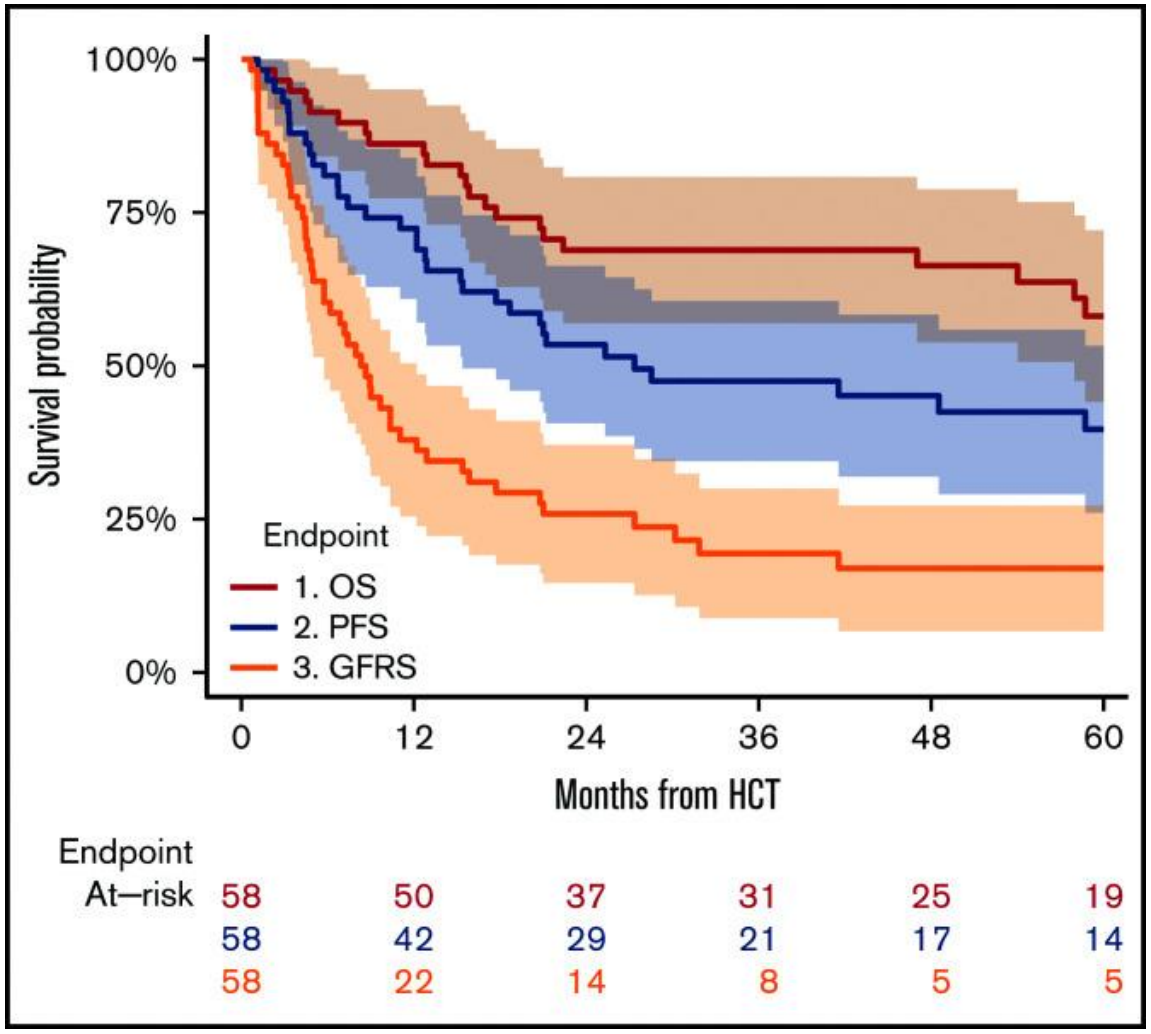
Nadeu F, Nat Med. 2022

RT has an immune suppressive microenvironment



Wang Y, Blood Cancer J. 2021
Gould C, Br J Haematol. 2021

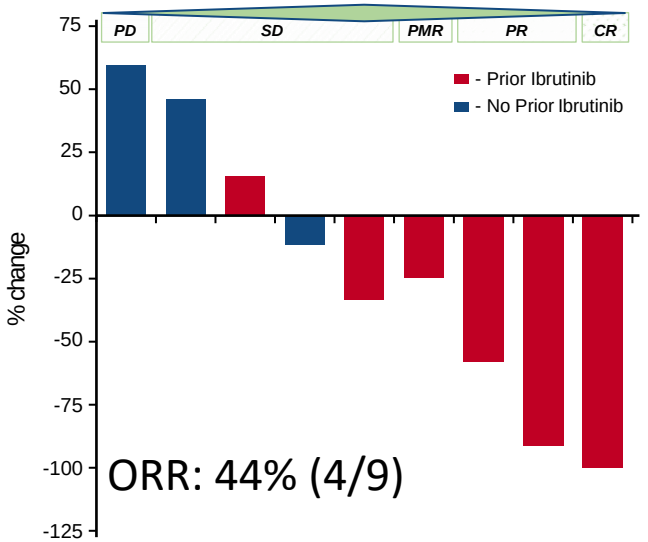
Allo SCT in RT

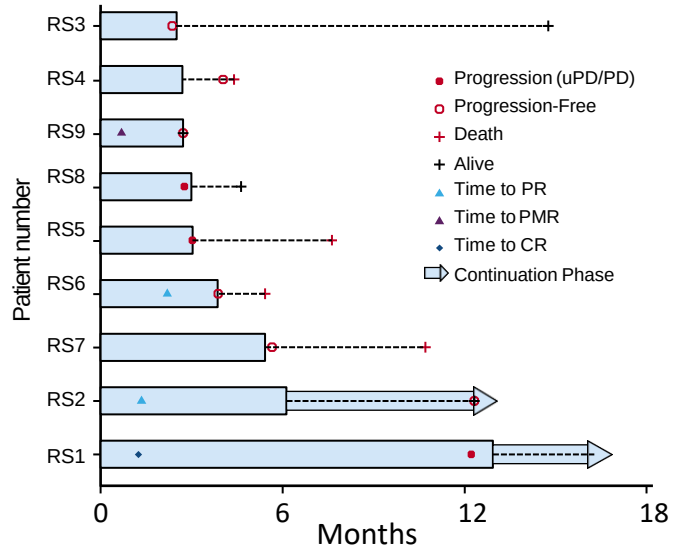


Lahoud OB, Blood Adv. 2021

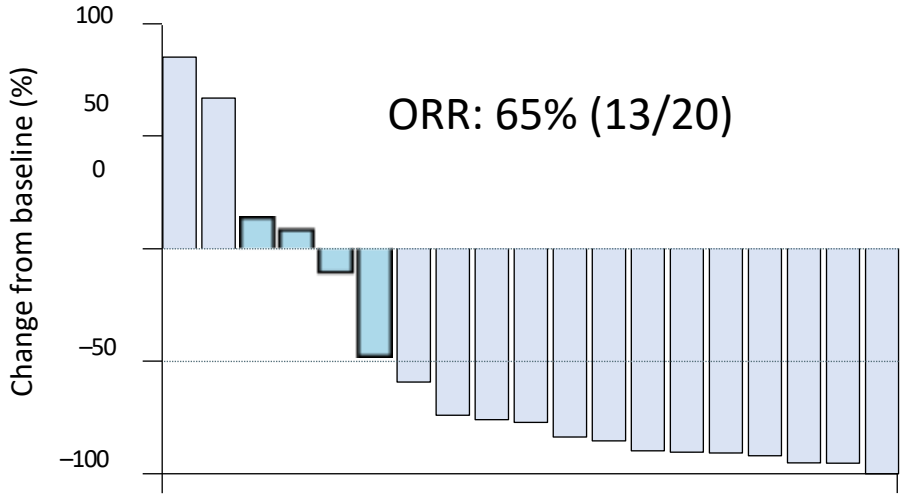
Immune checkpoint inhibitors in RT

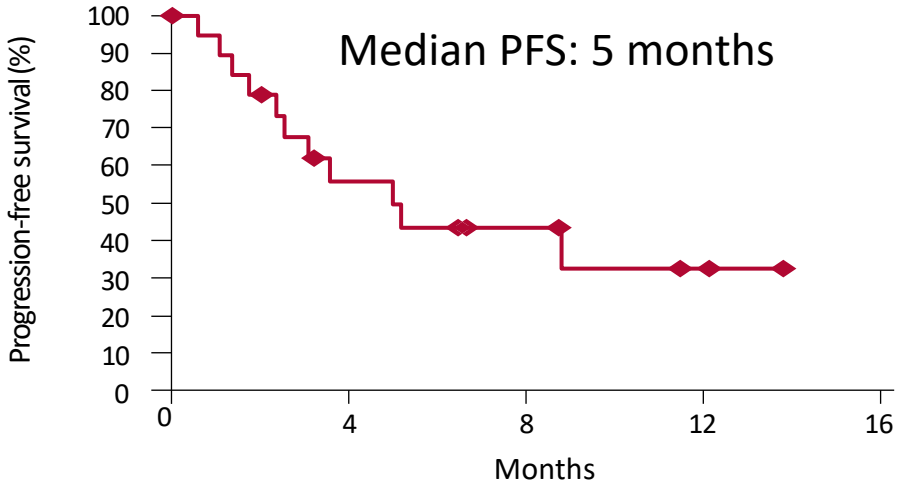
Pembrolizumab (n=9)





Nivolumab-Ibrutinib (n=20)





Ding W, et al. Blood. 2017; Younes A, et al. Lancet Haematol. 2019

MOLTO: international phase II study on venetoclax, obinutuzumab, atezolizumab in treatment naive DLBCL-RT

REL RETE EMATOLOGICA LOMBARDA

IELSG

Data cut-off: Feb 2023

Key inclusion

- **DLBCL** type RT
- ≥18 yrs
- ECOG<3
- Previously **UNtreated** RT

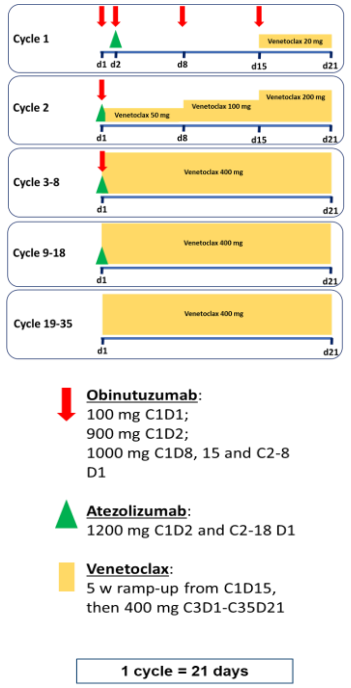
(may have been treated for CLL)

Key exclusion

- CNS localization
- No prior atezo, obi or venetoclax
- No history of autoimmune disease

28 pts
First 9 incl in the safety-run phase

1° pts-in: Oct 2019
Last pts-in: Oct 2022



Primary Endpoint:
ORR >67% after 6 cycles

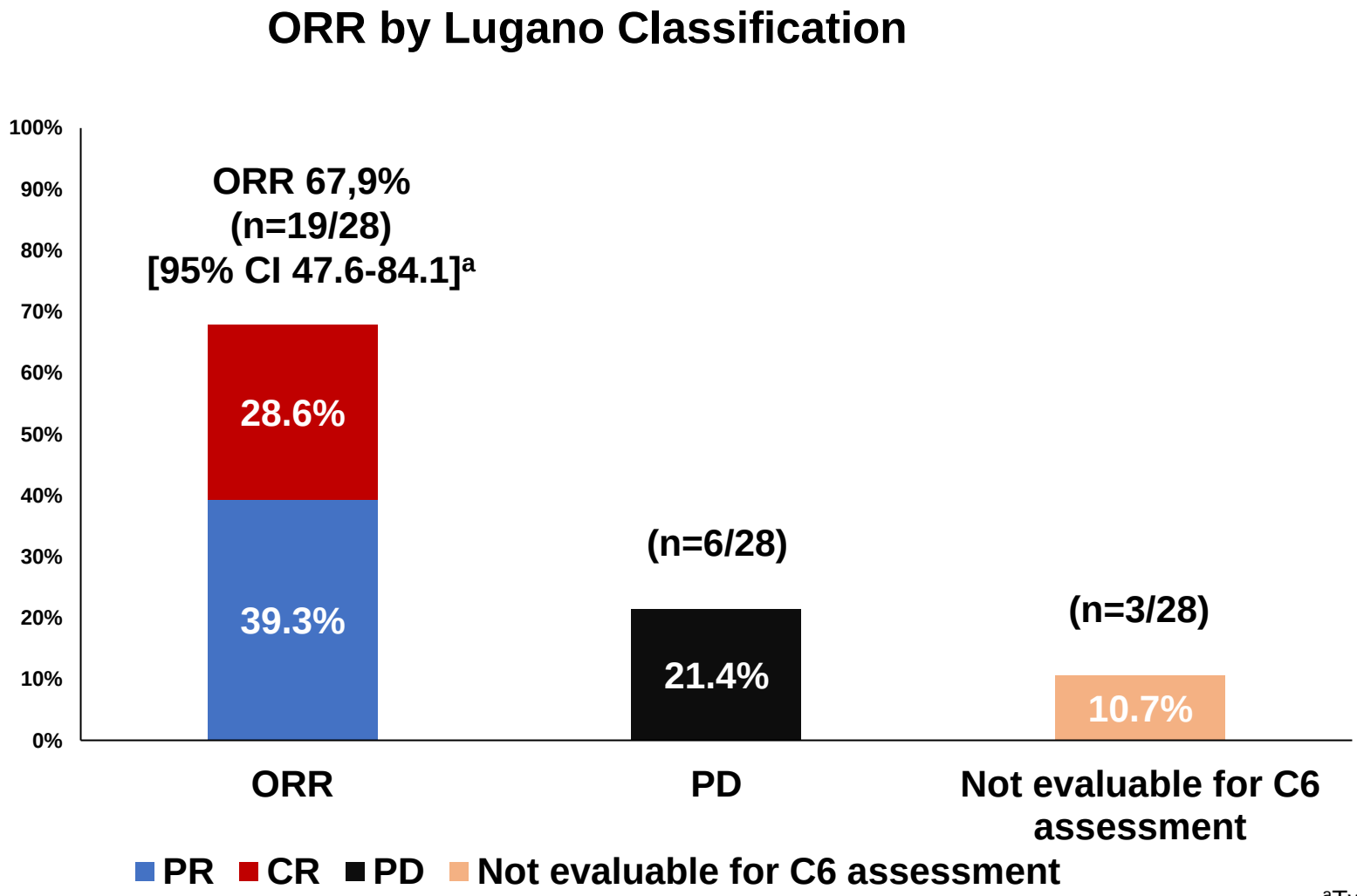
Secondary Endpoints:
- AEs, SAEs, immune-related AEs
- CRR
- PFS, OS, DOR

Exploratory Objectives:
- Correlation of biologic markers with ORR and PFS
- MRD monitoring

Histology centrally revised

Frustaci AM; ASCO 2022

Treatment response at Cycle 8 (ITT)



[a]Two-sided Clopper–Pearson, 95% CI

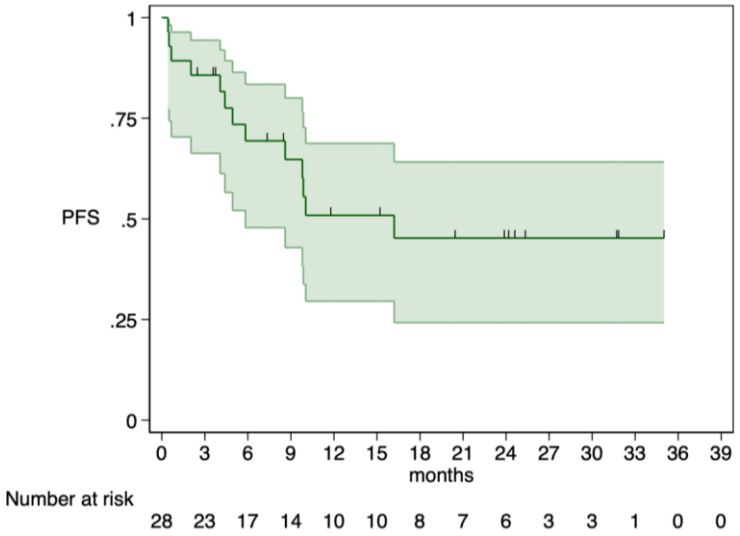
Frustaci AM; ASCO 2022

Survival outcomes

Median follow-up: 11.6 months (range 0.5-37.3 months)

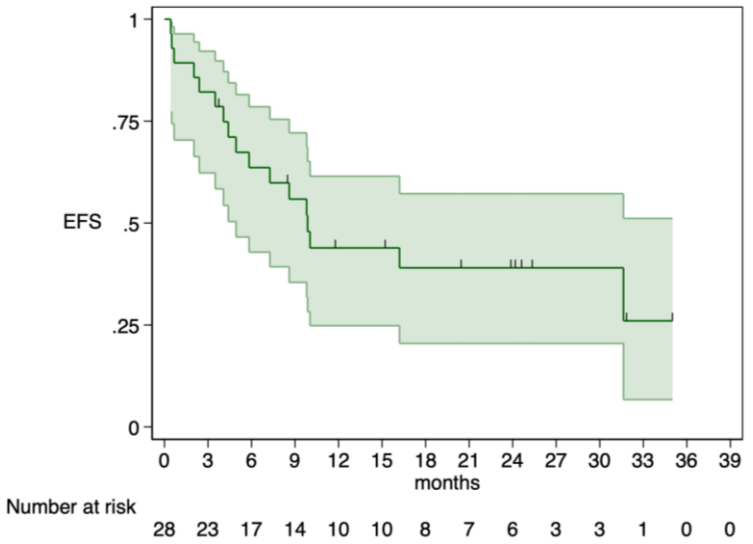
Time to Progression

12-mo TTP 50.9% [95%CI (29.6-68.8)]
(median 16.2 months)



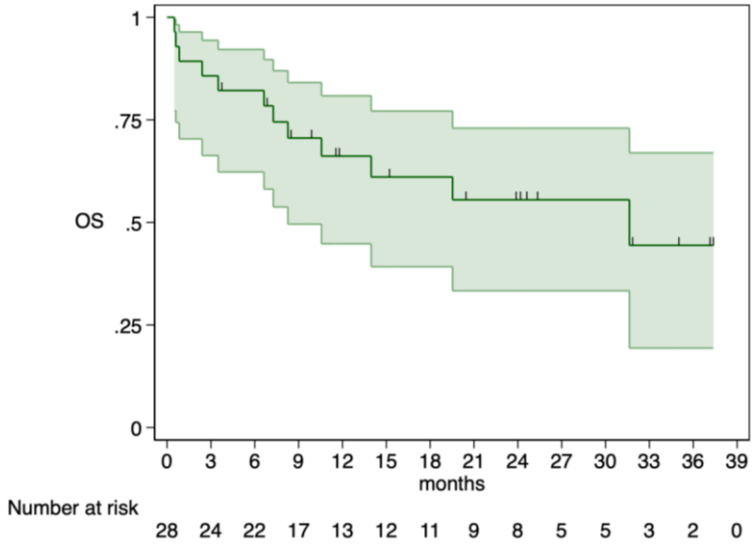
EFS

12-mo EFS 43.9% [95%CI (24.8-61.5)]
(median 9.9 months)



OS

12-mo OS 66.2% [95% CI (44.8.8-80.9)]
(median 31.6 months)



Frustaci AM; ASCO 2022

T-cell redirecting therapy in RT

	N. of patients	Product	ORR (N)	CR (N)
Ortiz-Maldonado V, 2022	9	ARI-0001	7	4
Kittai AS, 2020	9	Axi-cel	8	5
Bensaber H, 2022	14	Axi-cel or Loso-cel	6	5
Carlo-Stella C, 2022	11	Glofitamab	7	5
Kater AP, 2022	10	Epcoritamab	6	5

Summary

- Histologically aggressive CLL must be treated as a progressive, high risk CLL
- cHL arising in patients with CLL must be treated as de novo cHL
- Clonally unrelated LBCL arising in patients with CLL must be treated as de novo LBCL
- R-CHOP-like or venetoclax-R-CHOP-like are “SOC”
- Combination of pathway inhibitors with checkpoint inhibitors are promising
- T-cell engaging therapies are under development
- Allo SCT is the sole curative treatment